

## PERMEABLE REACTOR PLATE AND METHOD

## BACKGROUND OF THE INVENTION

The present invention relates to a reactor plate and method for running multiple parallel screening reactions with multiphase reactant systems.

In experimental reaction systems, each potential combination of reactant, catalyst and condition must be evaluated in a manner that provides correlation to performance in a production scale reactor. Combinatorial organic synthesis (COS) is a high throughput screening (HTS) methodology that was developed for pharmaceuticals. COS uses systematic and repetitive synthesis to produce diverse molecular entities formed from sets of chemical "building blocks." As with traditional research, COS relies on experimental synthesis methodology. However instead of synthesizing a single compound, COS exploits automation and miniaturization to produce large libraries of compounds through successive stages, each of which produces a chemical modification of an existing molecule of a preceding stage. A library is a physical, trackable collection of samples resulting from a definable set of processes or reaction steps. The libraries comprise compounds that can be screened for various activities.

The technique used to prepare such libraries involves a stepwise or sequential coupling of building blocks to form the compounds of interest. For example, Pirrung *et al.*, U.S. Pat. 5,143,854 discloses a technique for generating arrays of peptides and other molecules using light-directed, spatially-addressable synthesis techniques. Pirrung *et al.* synthesizes polypeptide arrays on a substrate by attaching photoremovable groups to the surface of the substrate, exposing selected regions of the substrate to light to activate those regions, attaching an amino acid monomer with a photoremovable group to the activated region and repeating the steps of activation and attachment until polypeptides of desired lengths and sequences are synthesized.

Combinatorial high throughput screening (CHTS) is an HTS methodology that incorporates characteristics of COS. The definition of the experimental space permits a CHTS investigation of highly complex systems. The method selects a best case set of factors of a chemical reaction. The method comprises defining a chemical experimental space by (i) identifying relationships

between factors of a candidate chemical reaction space; and (ii) determining a chemical experimental space comprising a table of test cases for each of the factors based on the identified relationships between the factors with the identified relationships based on researcher specified n-tuple combinations between identities of the relationships. A CHTS method is effected on the chemical experimental space to select a best case set of factors.

The methodology of COS is difficult to apply in certain reaction systems. For example up to now, COS has not been applied to systems that may produce vaporous products that may escape from respective cells of an array and contaminate the contents of adjacent or near-by cells. There is a need for improved reaction plate and method to permit rapid and effective investigation of vaporous product reaction systems.

## BRIEF SUMMARY OF THE INVENTION

The invention provides a reactor plate and method to investigate these types of systems. According to the invention, a reactor plate comprises a substrate with an array of reaction cells and a permeable film covering at least one of the cells to selectively permit transport of a reactant gas into the one cell while preventing transport of a reaction product out of the cell.

A method comprises providing a reactor plate comprising a substrate with an array of reaction cells, at one least one cell of the array comprising a cavity and a permeable film cover and conducting a combinatorial high throughput screening (CHTS) method with the reactor plate.

## BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a schematic representation of a top view of a reactor plate according to the invention;

FIG. 2 is a schematic cut-away front view through line A-A of the reactor plate of FIG. 1;

FIGs. 3 to 5 are schematic cut-away representations of various cell configurations;

FIG. 6 is a graph of permeability versus film thickness;

FIG. 7 is a graph of permeability versus temperature; and

FIG. 8 is a 3-D column graph showing interactions of transition metal cocatalysts with lanthanide metal cocatalysts.

## DETAILED DESCRIPTION OF THE INVENTION

In an embodiment, the invention is directed to a reactor plate and method for CHTS. The method and system of the present invention can be useful for parallel high-throughput screening of chemical reactants, catalysts, and related process conditions.

Typically, a CHTS method is characterized by parallel reactions at a micro scale. In one aspect, CHTS can be described as a method comprising (A) an iteration of steps of (i) selecting a set of reactants; (ii) reacting the set and (iii) evaluating a set of products of the reacting step and (B) repeating the iteration of steps (i), (ii) and (iii) wherein a successive set of reactants selected for a step (i) is chosen as a result of an evaluating step (iii) of a preceding iteration.

In another typical CHTS method, a multiplicity of tagged reactants is subjected to an iteration of steps of (A) (i) simultaneously reacting the reactants, (ii) identifying a multiplicity of tagged products of the reaction and (B) evaluating the identified products after completion of a single or repeated iteration (A).

A typical CHTS can utilize advanced automated, robotic, computerized and controlled loading, reacting and evaluating procedures.

These and other features will become apparent from the drawings and following detailed discussion, which by way of example without limitation describe preferred embodiments of the present invention.

FIG. 1 shows a top view of a preferred reactor plate and FIG. 2 shows a cut-away front view through line A-A of the plate of FIG. 1. FIG. 1 and FIG. 2 show reactor plate 10 that includes an array 12 of reaction cells 14 embedded into a supporting substrate 16 of the plate 10. Each cell 14 is shown covered with a permeable film 18. Each cell 14 can be covered with the same film 18 or each cell can be covered with a different film to provide different reaction characteristics to different cells 14. Further, in another embodiment, selected cells 14 can be covered

with film while other cells 14 are left uncovered to provide still different reaction characteristics.

FIGs. 3, 4 and 5 illustrate embodiments of the cell of the invention.

FIG. 3 shows a shallow cell with permeable film cover. For example, the cell can have a volume of about  $20 \text{ mm}^3$ , a film area of  $20 \text{ mm}^2$ , a 1 mil film and a 1 mm deep cavity. FIG. 4 shows a cell with two opposing walls comprising permeable film. For example, the cell can have a volume of about  $20 \text{ mm}^3$ , a film area of  $40 \text{ mm}^2$ , a 1 mil film and a 1 mm deep cavity. FIG. 5 shows a concave bottomed cell with permeable film cover. For example, the cell can have a volume of about  $40\text{-}50 \text{ mm}^3$ , a film area of  $2\text{-}3 \text{ mm}^2$ , a 1 mil film and a 5 mm deep cavity. The respective cells and films are selected by considering permeability of the film and robustness and rate of the reaction. For example, the cells can be designed so that rate of diffusion of gas through the membrane is greater than the rate of gas uptake of the reaction. In this instance, the system would be "reaction-limited" rather than "diffusion-limited."

The film 18 can be any permeable film that will selectively admit transport of a reactant but will prohibit transport of a reaction product in a CHTS process. For example, the film can be a polycarbonate, perfluoroethylene, polyamide, polyester, polypropylene, polyethylene or a monofilm, coextrusion, composite or laminate.

Polycarbonate, PET and polypropylene are preferred films. Relative humidity may affect permeability of many films. However, permeability of polycarbonate, PET and polypropylene is substantially unaffected by changes in humidity. Hence, these films are particularly advantageous to conduct reactions in humid conditions or to conduct moisture sensitive reactions such as a carbonylation reaction.

In certain applications, the film can be characterized by a diffusion coefficient of about  $5 \times 10^{-10}$  to about  $5 \times 10^{-7}$ , desirably about  $1 \times 10^{-9}$  to about  $1 \times 10^{-7}$  and preferably about  $2 \times 10^{-8}$  to about  $2 \times 10^{-6}$  in units of  $\text{cc(STP)-mm/cm}^2\text{-sec-cmHg}$ .

The permeability of a film will vary with thickness. In this invention, the film can be of any thickness that will admit transport of a reactant, usually a gas or vapor, but that will prohibit transport of a reaction product. The thickness of the film

can be about .0002 to about .05 mm, desirably about .005 to about .04 mm and preferably about .01 to about .025 mm. FIG. 6 shows CO<sub>2</sub> permeability of a polycarbonate film with thickness at 75°F and 0% relative humidity, where permeability (P) equals cc/100 in<sup>2</sup>-atm-day

Temperature is another variable that can affect film permeability. FIG. 7 shows the effect of temperature on the permeability of 1 mil blown polycarbonate film at constant relative humidity (RH). FIG. 7 shows permeability versus thickness at 75°F and 0% relative humidity where P equals cc/100 in<sup>2</sup>-atm-day. Accordingly, the CHTS method can comprise reacting a reactant at a temperature of about 0 to about 150°C, desirably about 50 to about 140°C and preferably about 75 to about 125°C.

In one embodiment, the invention is applied to study a process for preparing diaryl carbonates. Diaryl carbonates such as diphenyl carbonate can be prepared by reaction of hydroxyaromatic compounds such as phenol with oxygen and carbon monoxide in the presence of a catalyst composition comprising a Group VIIIIB metal such as palladium or a compound thereof, a bromide source such as a quaternary ammonium or hexaalkylguanidinium bromide and a polyaniline in partially oxidized and partially reduced form. The invention can be applied to screen for a catalyst to prepare a diaryl carbonate by carbonylation.

Various methods for the preparation of diaryl carbonates by a carbonylation reaction of hydroxyaromatic compounds with carbon monoxide and oxygen have been disclosed. The carbonylation reaction requires a rather complex catalyst. Reference is made, for example, to Chaudhari *et al.*, U.S. Pat. 5,917,077. The catalyst compositions described therein comprise a Group VIIIIB metal (i.e., a metal selected from the group consisting of ruthenium, rhodium, palladium, osmium, iridium and platinum) or a complex thereof.

The catalyst material also includes a bromide source. This may be a quaternary ammonium or quaternary phosphonium bromide or a hexaalkylguanidinium bromide. The guanidinium salts are often preferred; they include the  $\alpha$ ,  $\omega$ -bis(pentaalkylguanidinium)alkane salts. Salts in which the alkyl groups contain 2-6 carbon atoms and especially tetra-n-butylammonium bromide and hexaethylguanidinium bromide are particularly preferred.

Other catalytic constituents are necessary in accordance with Chaudhari *et al.* The constituents include inorganic cocatalysts, typically complexes of cobalt(II) salts with organic compounds capable of forming complexes, especially pentadentate complexes. Illustrative organic compounds of this type are nitrogen-heterocyclic compounds including pyridines, bipyridines, terpyridines, quinolines, isoquinolines and biquinolines; aliphatic polyamines such as ethylenediamine and tetraalkylethylenediamines; crown ethers; aromatic or aliphatic amine ethers such as cryptanes; and Schiff bases. The especially preferred inorganic cocatalyst in many instances is a cobalt(II) complex with bis-3-(salicylamino)propylmethylamine.

Organic cocatalysts may be present. These cocatalysts include various terpyridine, phenanthroline, quinoline and isoquinoline compounds including 2,2':6',2''-terpyridine, 4-methylthio-2,2':6',2''-terpyridine and 2,2':6',2''-terpyridine N-oxide, 1,10-phenanthroline, 2,4,7,8-tetramethyl-1,10-phenanthroline, 4,7-diphenyl-1,10-phenanthroline and 3,4,7,8-tetramethyl-1,10-phenanthroline. The terpyridines and especially 2,2':6',2''-terpyridine are preferred.

Another catalyst constituent is a polyaniline in partially oxidized and partially reduced form.

Any hydroxyaromatic compound may be employed. Monohydroxyaromatic compounds, such as phenol, the cresols, the xylenols and p-cumylphenol are preferred with phenol being most preferred. The method may be employed with dihydroxyaromatic compounds such as resorcinol, hydroquinone and 2,2-bis(4-hydroxyphenyl)propane or "bisphenol A," whereupon the products are polycarbonates.

Other reagents in the carbonylation process are oxygen and carbon monoxide, which react with the phenol to form the desired diaryl carbonate.

These and other features will become apparent from the following detailed discussion, which by way of example without limitation describes a preferred embodiment of the present invention.

#### Example

This example illustrates the identification of an active and selective catalyst for the production of aromatic carbonates. The procedure identifies the best

catalyst from within a complex chemical space, where the chemical space is defined as an assemblage of all possible experimental conditions defined by a set of variable parameters such as formulation ingredient identity or amount.

In this Example, a reactor plate is designed to provide a rate of diffusion of reactant gas through a polymer membrane greater than the rate of reaction of the gas to form the desired product. The desired reaction rate of the catalyst is 1 gram-mole/liter-hour. Each cell in the array of the plate is 5 mm in diameter and 1 mm thick, with 0.01 mm film making up the top and bottom of each cell as illustrated in FIG. 4. This design provides a cell volume of 20 mm<sup>3</sup> and a film area of 40 mm<sup>2</sup>.

The plate is prepared for reaction by providing a preformed 86x126 mm piece of 1 mm polycarbonate substrate with an 8x12 array of 5-mm holes and heat sealing a piece of 86 x 126 mm 0.01 mm thick polycarbonate film to the substrate bottom. Twenty (20) microliters of premixed catalyst solution is delivered to each cell. A second 86x126mm piece of .01 mm polycarbonate film is heat sealed to the top of the plate substrate.

The subsequent reaction is run at 100°C and at a partial pressure of 10 atmospheres of O<sub>2</sub>. Permeability of the film to oxygen at 100°C is calculated to be 5x10<sup>-9</sup> cc(STP)-mm/cm<sup>2</sup>-sec-cmHg. Oxygen flow through the film is calculated as 2.44x10<sup>-05</sup> gram/moles-hour to provide an oxygen delivery rate to the 20 mm<sup>3</sup> (2x10<sup>-5</sup> liters) reaction volume of 1.22 g-mols/liter-hour. Formulation parameters are given in TABLE 1.

TABLE 1

	Formulation Type Parameter Variation	Formulation Amount Parameter Variation
Precious metal catalyst	Held Constant	Held Constant
Transition Metal Cocatalyst (TM)	Ti, V, Cr, Mn, Fe, Co, Ni, Cu (as their acetylacetonates)	5 (as molar ratios to precious metal catalyst)
Lanthanide Metal Cocatalyst (LM)	La, Ce, Eu, Gd (as their acetylacetonates)	5 (as molar ratios to precious metal catalyst)
Cosolvent (CS)	Dimethylformamide (DMFA), Dimethylacetamide (DMAA), Diethyl acetamide (DEAA)	500 (as molar ratios to precious metal catalyst)
Hydroxyaromatic compound	Held constant	Sufficient added to achieve constant sample volume

The size of the initial chemical space defined by the parameters of TABLE 1 is 96 possibilities. This is a large experimental space for a conventional technique. However, the experiment can be easily conducted according to the present invention to determine optimal compositions. The space is explored using a full factorial design. A full factorial design of experiment (DOE) measures the response of every possible combination of factors and factor levels. These responses can be analyzed to provide information about every main effect and every interaction effect. The design is given in TABLE 2, below.

In this experiment, each metal acetylacetonate and each cosolvent were made up as stock solutions in phenol. Ten ml of each stock solution are produced by manual weighing and mixing. For each sample, an appropriate quantity of each stock solution is then combined using a Hamilton MicroLab 4000 laboratory robot into a single 2-ml vial. The mixture is stirred using a miniature magnetic stirrer. Then 20 microliter aliquots are measured out by the robot to individual cells in the array. After the aliquots are distributed, the upper film is heat sealed to the substrate.

The assembled reactor plate is then placed in an Autoclave Engineers 1-gallon autoclave, which is then pressurized to 1500 psi (100 atm) with a 10% O<sub>2</sub> in CO mixture. This provides a 10 atm oxygen partial pressure. the autoclave is heated to 100°C for two hours, cooled, depressurized and the array removed. Raman spectrum of each product is taken by focussing an argon ion laser 38 (Spectra Physics 2058) on a cell and detecting the inelastically scattered light with an Acton Spectra-Pro 300I spectrophotometer 36.

Performance in this example is expressed numerically as a catalyst turnover number or TON. TON is defined as the number of moles of aromatic carbonate produced per mole of charged palladium catalyst. The performance of each of the runs is given in the column "TON" of TABLE 2.



TABLE 2

Run	Transition Metal (TM) Cocatalyst	Lanthanide Metal (LM) Cocatalyst	Cosolvent (CS)	TON
1 Mn		Gd	DEAA	555.1078
2 Cu		La	DMAA	456.5777
3 Mn		Ce	DMAA	513.6325
4 Ti		Gd	DEAA	400.5089
5 V		Eu	DMFA	587.5912
6 Mn		La	DMAA	1750.03
7 Ti		Ce	DEAA	292.4069
8 Cr		Eu	DMAA	625.9431
9 V		Ce	DMFA	665.1948
10 Fe		Eu	DMFA	332.9006
11 Ti		Eu	DMFA	679.5486
12 Fe		La	DEAA	468.5033
13 Co		Ce	DEAA	257.2479
14 Cu		Eu	DMAA	468.7711
15 Ni		Ce	DMFA	433.6684
16 Co		Gd	DMAA	485.2293
17 Cu		Gd	DEAA	342.2256
18 Cu		Gd	DMFA	506.5736
19 Mn		Eu	DMFA	356.3573
20 Co		La	DMFA	545.6339
21 Ni		Gd	DMFA	483.2507
22 V		Gd	DMFA	590.907
23 Ti		La	DEAA	885.7548
24 Cr		Eu	DEAA	344.2193
25 Mn		Gd	DMFA	338.4866
26 Fe		Ce	DMFA	474.0333
27 Ni		Eu	DMFA	758.6696
28 Mn		Ce	DMFA	625.6508
29 Cr		Gd	DMFA	603.5539
30 Cr		Eu	DMFA	249.9745
31 Co		Eu	DEAA	431.0617
32 Mn		Gd	DMAA	372.3904
33 Ni		Gd	DMAA	652.7145
34 Cu		Ce	DMAA	352.7221
35 Ni		Eu	DEAA	459.774
36 Co		Gd	DEAA	472.6578
37 Fe		La	DMFA	472.984
38 V		La	DMAA	858.9171
39 V		Eu	DMAA	416.1047
40 Cu		La	DEAA	345.512
41 Cr		La	DMFA	552.11
42 Cu		Eu	DEAA	250.3933
43 Cr		La	DEAA	417.1977
44 Mn		La	DEAA	1291.111
45 V		Gd	DEAA	490.6305
46 Co		Gd	DMFA	452.9355
47 V		Gd	DMAA	413.9911

48 Cu	Gd	DMAA	683.2233
49 Fe	Ce	DEAA	276.7799
50 Co	La	DEAA	390.3853
51 Ti	Gd	DMAA	390.6338
52 Ni	La	DMAA	673.2558
53 Mn	Ce	DEAA	360.0271
54 V	Ce	DMAA	650.6003
55 V	La	DMFA	848.4497
56 Cu	La	DMFA	476.2182
57 Cr	Gd	DMAA	427.1539
58 Co	Ce	DMFA	468.8664
59 V	La	DEAA	743.0518
60 Co	Eu	DMAA	364.7413
61 Fe	Eu	DMAA	572.7474
62 V	Eu	DEAA	459.1624
63 Ti	La	DMFA	778.1048
64 Ni	Gd	DEAA	522.5839
65 Fe	Gd	DMAA	340.3491
66 Ni	La	DMFA	733.7841
67 Cr	La	DMAA	613.4944
68 V	Ce	DEAA	295.7852
69 Ni	Eu	DMAA	868.0304
70 Fe	La	DMAA	559.6479
71 Fe	Gd	DMFA	592.372
72 Cr	Ce	DEAA	326.6567
73 Cr	Ce	DMAA	417.9809
74 Cu	Ce	DEAA	267.8915
75 Ni	Ce	DEAA	262.121
76 Ni	Ce	DMAA	554.9479
77 Cr	Ce	DMFA	495.3985
78 Ni	La	DEAA	451.5785
79 Ti	Eu	DMAA	877.8409
80 Fe	Ce	DMAA	612.9162
81 Mn	Eu	DMAA	644.8604
82 Fe	Gd	DEAA	521.141
83 Fe	Eu	DEAA	457.5463
84 Mn	La	DMFA	1650.954
85 Ti	Eu	DEAA	450.2065
86 Ti	Ce	DMAA	512.3347
87 Cu	Ce	DMFA	324.8884
88 Ti	Gd	DMFA	747.381
89 Co	Ce	DMAA	242.6424
90 Co	La	DMAA	366.3668
91 Co	Eu	DMFA	474.389
92 Ti	Ce	DMFA	374.0002
93 Cu	Eu	DMFA	549.2309
94 Cr	Gd	DEAA	279.3706
95 Ti	La	DMAA	634.0476
96 Mn	Eu	DEAA	350.5033

The results are analyzed using a "General Linear Model" routine in Minitab software. The routine is set to calculate an Analysis of Variance (ANOVA) for all main effects and 2-way interactions. The ANOVA is given in TABLE 3. In TABLE 3, Sources of Variation are potentially significant factors and interactions. Degrees of Freedom are a measure of the amount of information available for each source. Adjusted Sums of Squares are the squares of the deviations caused by each source. Adjusted Mean Squares are Adjusted Sums/Degrees of Freedom. The F Ratio is the Adjusted Mean Square for each Source/Adjusted Mean Square for Error. The F ratio is compared to a standard table to determine its statistical significance at a given probability (0.001 or 0.1% in this case).

TABLE 3

Source of Variation	Degrees of Freedom	Adjusted Sums of Squares	Adjusted Mean Squares	F Ratio	Significant at P < 0.001
TM	7	1243723	177675	9.84	Yes
LM	3	973525	324508	17.98	Yes
CS	2	896969	448484	24.84	Yes
TM*LM	21	1754525	83549	4.63	Yes
TM*CS	14	353434	25245	1.4	No
LM*CS	6	205012	34169	1.89	No
Error	42	758191	18052		
Total	95				

The column "Significant at P<.001" indicates that a TM\*LM (transition metal \*lanthanide metal) interaction has a significant effect on TON. These interactions are also illustrated in FIG. 8, which shows that interaction of Mn and La have a strong positive influence on the TON.

While preferred embodiments of the invention have been described, the present invention is capable of variation and modification and therefore should not be limited to the precise details of the Example. The invention includes changes and alterations that fall within the purview of the following claims.